

**IN THE SPECIFICATION:**

Please amend the specification as follows:

Please delete the paragraph on page 4, lines 10-15, and replace it with the following paragraph:

In this connection, preference is given to digoxigenin-binding muteins which have an amino acid substitution at at least 4 to 7 or, preferably, at least 8 to 12 of the sequence positions defined above. A particularly preferred mutein is the polypeptide which has the amino acid sequence encoded by ~~depicted as~~ SEQ ID NO. 15.

Please delete the paragraph on page 8, lines 1-18, and replace it with the following paragraph:

Particularly preferred muteins of the invention carry, when compared to the bilin-binding protein, at least one, at least 4 to 7, or, preferably, at least 8 to 12 of the amino acid substitutions selected from Glu(28)->Gln, Lys (31)->Ala, Asn(34)->Asp, Ser(35)->His, Val(36)->Ile, Glu(37)->Thr, Asn(58)->Arg, His(60)->Ser, Ile(69)->Ser, Leu(88)->Tyr, Tyr(90)->Ile, Lys(95)->Gln, Asn(97)->Gly, Tyr(114)->Phe, Lys(116)->Ser, Gln(125)->Met and Phe(127)->Leu. The representation chosen indicates in each case first the amino acid in the natural bilin-binding protein (SWISS-PROT database accession code P09464, SEQ ID NO: 28) together with the sequence position for the mature polypeptide in brackets, and the corresponding amino acid in a mutein of the invention is stated after the arrow. Very particularly preferred muteins according to this invention carry all of the amino acid substitutions mentioned.

Please delete the paragraph on page 12, line 21, to page 13, line 4, and replace it with the following paragraph:

In another aspect, the present invention relates to a nucleic acid which comprises a sequence coding for a mutein or a fusion protein of a mutein of the bilin-binding protein. This

nucleic acid may be part of a vector on which an operatively functional environment for expressing the nucleic acid is present. A large number of suitable vectors is known from the prior art and is not described in detail here. An operatively functional environment means those elements which allow, assist, facilitate and/or increase transcription and/or subsequent processing of an mRNA. Examples of elements of this kind include promoters, enhancers, transcription initiation sites, and transcription termination sites, translation initiation sites, polyadenylation signals, etc. In a preferred embodiment, such nucleic acids of the invention comprise a nucleic acid sequence which encodes the polypeptide sequence depicted as SEQ ID NO: 23 45. Owing to the degeneracy of the genetic code, it is clear to the skilled worker that the nucleotide sequence stated as SEQ ID NO:15 represents only a single nucleotide sequence from the group of nucleotide sequences encoding the polypeptide according to SEQ ID NO: 23 45.

Please delete the paragraph on page 19, lines 9-31, and replace it with the following paragraph:

Figure 2 shows a drawing of the expression vectors pBBP27 (A) and pBBP29 (B). pBBP27 codes for a fusion protein of bacterial alkaline phosphatase with its own signal sequence, a peptide linker having the sequence Pro-Pro-Ser-Ala (SEQ ID NO: 29), the mutein DigA16 and also the Strep- tag II affinity tag. The corresponding structural gene is followed by the dsbC structural gene (including its ribosomal binding site) from E. coli (Zapun et al., Biochemistry 34 (1995), 5075-5089) as second cistron. The artificial operon formed in this way is under joint transcriptional control of the tetracycline promoter/operator (tetp/o) and ends at the lipoprotein transcription terminator (t1pp). Further vector elements are the origin of replication (ori), the intergenic region of filamentous bacteriophage f1 (f1-IG), the ampicillin resistance gene (bla) coding for  $\beta$ -lactamase and the tetracycline repressor gene (tetR). pBBP29 codes for a fusion protein of the OmpA signal sequence, the mutein DigA16, the Strep-tag II affinity tag, a peptide linker consisting of five glycine residues, and bacterial alkaline phosphatase without its N-terminal amino acid arginine. The vector elements outside this region are identical to vector pBBP27.

Please delete the paragraph on page 22, lines 4-14, and replace it with the following paragraph:

A relevant section of the pBBP20 nucleic acid sequence is shown together with the encoded amino acid sequence as SEQ ID NO:1 and 19, respectively, in the sequence listing. The section starts with a hexanucleotide sequence which was obtained by ligating an *Xba*I overhang with an *Spe*I overhang complementary thereto and ends with the *Hind*III cleavage site. The vector elements outside this region are identical to vector pASK75 whose complete nucleotide sequence is stated in the German Offenlegungsschrift DE 44 17 598 A1.

Please delete the paragraph on page 28, lines 15-25, and replace it with the following paragraph:

In order to be able to produce the muteins of the bilin-binding protein as a fusion protein with the Strep-tag II and the albumin-binding domain, the gene cassette between the two *Bst*XI cleavage sites was subcloned from vector pBBP20 into vector pBBP22. A relevant section of the pBBP22 nucleic acid sequence is represented, together with the encoded amino acid sequence, as SEQ ID NO:9 and 20, respectively, in the sequence listing. The section starts with the *Xba*I cleavage site and ends with the *Hind*III cleavage site. The vector elements outside this region are identical to vector pASK75.

Please delete the paragraph on page 31, lines 5-21, and replace it with the following paragraph:

Four colonies from the upper membrane, which caused a distinct color signal, were used for preparing cultures in LB/Amp medium of 4 ml in volume. Their plasmid DNA was isolated with the aid of the JETquick Plasmid Miniprep Spin kit (Genomed) according to the manufacturer's instructions, and the gene section coding for the mutein was subjected to sequence analysis. Sequence analysis was carried out with the aid of the T7 sequencing kit (Pharmacia) according to the manufacturer's instructions by using oligodeoxynucleotides SEQ ID NO:10 and SEQ ID NO:11. It was found in the process that all four plasmids studied

carried the same nucleotide sequence. The corresponding gene product was denoted by DigA (SEQ ID NO:12). The DigA nucleotide sequence was translated into the amino acid sequence (SEQ ID NO: 21) and is represented in the sequence listing.

Please delete the paragraph on page 32, lines 11-21, and replace it with the following paragraph:

The pBBP24 vector DNA was cut with *Bst*XI accordingly and the 4028 bp fragment obtained was isolated. A relevant section of the pBBP24 nucleic acid sequence is represented, together with the encoded amino acid sequence, as SEQ ID NO:14 and 22, respectively, in the sequence listing. The section starts with the *Xba*I cleavage site and ends with the *Hind*III cleavage site. The vector elements outside this region are identical to vector pASK75. PBBP24 is virtually identical with pBBP20, wherein the BBP gene has been inactivated by means of appropriately introduced stop codons.

Please delete the paragraph on page 37, lines 19-27, and replace it with the following paragraph:

A relevant section of the pBBP21 nucleic acid sequence is represented, together with the encoded amino acid sequences, as SEQ ID NOS: 16, 24, and 25, respectively, in the sequence listing. The section starts with the *Xba*I cleavage site and ends with a hexanucleotide which was obtained by ligating a blunt strand end with a filled-up *Hind*III strand end, with the loss of the original *Hind*III cleavage site. The vector elements outside this region are identical to vector pASK75.

Please delete the paragraph on page 39, lines 20-34, and replace it with the following paragraph:

The ligand binding properties of muteins DigA, DigA16 and also of the recombinant bilin-binding protein (encoded by SEQ ID NO:16) were determined by means of the method of fluorescence titration. In this case, the decrease in intrinsic tyrosine and/or tryptophan

fluorescence of the protein forming a complex with the ligand was measured. The measurements were carried out in a fluorimeter, type LS 50 B (Perkin Elmer) at an excitation wavelength of 295 nm (slit width 4 nm) and an emission wavelength of 345 nm (slit width 6 nm). The ligands used were digoxigenin (Fluka), digoxin (Fluka), digitoxigenin (Fluka), digitoxin (Fluka), testosterone (Sigma), ouabain (Fluka), and 4-aminofluorescein (Fluka). The ligands showed no significant intrinsic fluorescence or absorption at the stated wavelength.

Please delete the paragraph on page 42, lines 4-14, and replace it with the following paragraph:

pBBP27 codes for a fusion protein of PhoA including the signal sequence thereof, a short peptide linker having the amino acid sequence Pro-Pro-Ser-Ala (SEQ ID NO: 29), the sequence corresponding to the mature DigA16 mutein and the Strep-tag-II. A relevant section of the pBBP27 nucleic acid sequence is represented, together with the encoded amino acid sequence, as SEQ ID NO:17 and 26, respectively, in the sequence listing. The section begins with the *Xba*I cleavage site and ends with the *Hind*III cleavage site. The vector elements outside this region are identical to vector pBBP21.

Please delete the paragraph on page 42, lines 16-26, and replace it with the following paragraph:

pBBP29 codes for a fusion protein of DigA16 with preceding OmpA signal sequence, followed by the peptide sequence for Strep-tag II, a sequence of 5 glycine residues and the mature PhoA sequence without the N-terminal amino acid arginine. A relevant section of the pBBP29 nucleic acid sequence is represented, together with the encoded amino acid sequence, as SEQ ID NO:18 and 27, respectively, in the sequence listing. The section begins with the *Xba*I cleavage site and ends with the *Hind*III cleavage site. The vector elements outside this region are identical to vector pBBP21.

**SEQUENCE LISTING:**

The present specification contains a Sequence Listing, which is submitted herewith on paper and considered part of this amendment. The as-filed application contained the data for the Sequence Listing. No new matter has been added. The same Sequence Listing is also submitted herewith on CRF diskette. The Office is requested to place the Sequence Listing at the appropriate spot in the specification, i.e., before the claims and starting on its own page under the section titled "Sequence Listing."